REMARKS

Status of the Claims

Claims 1, 6-13 and 26-30 are pending. Claims 2-5, and 14-25 are cancelled.

Applicants have amended claims 1, and 27-30 by inserting "wherein the ibuprofen is not enterically coated." Support for bilayer caplets comprising ibuprofen and diphenhydramine wherein the ibuprofen is not enterically coated can be found in the specification, and these amendments do not add new matter. Example 2 provides a detailed disclosure for the manufacture of the bilayer caplets of the invention, including step-by-step instructions for preparing the ibuprofen. This disclosure does not indicate that the ibuprofen is enterically coated. In addition, the specification describes variations of the formulation, such as changing the dose for patients sensitive to the medication, rather than enteric coating. See *specification*, p. 11, lines 14-15. The absence of enteric coating also finds inherent support in the nature of the invention. The specification states that "[w]hile not wishing to be bound by theory, the beneficial impact of the combination treatment relies on the rapid impact of ibuprofen due to is pharmacokenetic profile, and continuing effects of both ibuprofen and diphenhydramine." Specification, p. 16, line 20 to page 27, line 3. Enteric coating, which must dissolve before the ibuprofen is released, would delay the onset of ibuprofen's activity and thus would deprive the claimed formulation of its ability to rapidly induce sleep. As the claimed composition is an aid for more rapidly falling asleep enteric coating would inconsistent with this goal.

Applicants respectfully request reconsideration and examination of this application and the timely allowance of the pending claims in view of the arguments below.

Obviousness Rejections Under 35 USC § 103

Rejection of Gel Capsule Claims

The Office rejects claims 6-13 and 26 under 35 USC § 103(a) as allegedly unpatentable over U.S. Patent No. 4,522,826 ("*Sunshine*") in view of U.S. Patent No. 5,431,916 ("*White*"). The Office continues to assert that *Sunshine* teaches that polyethylene glycol "is a suitable binder to be employed in the composition comprising ibuprofen and diphenhydramine and additionally White also teaches that polyethylene glycol is suitable in the composition comprising ibuprofen and diphenhydramine because polyethylene glycol facilitates the solubility of actives." Office action, p. 9. The Office concludes that one of ordinary skill in the art would be motivated to select polyethylene glycol for inclusion in a composition comprising ibuprofen and diphenhydramine. *Id.* at 3-4.

Applicants respectfully traverse the obviousness rejection of claims 6-13 and 26. A proper *prima facie* obviousness rejection requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim

limitations. *See* M.P.E.P. § 2143. The Examiner bears the burden of establishing *prima facie* obviousness. *See* M.P.E.P. § 2142.

The Examiner has failed to establish *prima facie* obviousness as *Sunshine* and *White* fail to provide motivation to modify or combine their teachings. In particular, no motivation is provided for selecting polyethylene glycol, which appears in a laundry list of compounds in *Sunshine*, and both *Sunshine* and *White* teach away from inclusion of polyethylene glycol in a composition comprising ibuprofen and diphenhydramine.

The mere mention of polyethylene glycol in *Sunshine* does not render the instant invention obvious. As recognized by the Federal Circuit "virtually all inventions are combinations of old elements . . . . If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue." *See*, for example, *In re Rouffet*, 149 F.3d 1350, 1356, 47 U.S.P.Q.2d 1453, 1459 (Fed. Cir. 1998). Moreover, a prior art reference containing a "needle-in-the-haystack" type disclosure does not render a patent obvious. *See*, for example, *In re Luvisi*, 342 F.2d 102, 105, 144 U.S.P.Q. 646, 649 (C.C.P.A. 1965) ("Luvisi"). In *Luvisi*, the court reversed the Board's finding of obviousness because there was nothing in the references relied on by the Examiner that would suggest the selection of one compound from a list of around fifty compounds. *Id.*

In *Sunshine*, polyethylene glycol is one compound in a laundry list of "[s]uitable binders" including the following species and genuses:

> *starch*, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and *waxes*.

Sunshine, col. 7, lines 30-33 (emphasis added). This laundry list includes several genuses of binders (e.g., starch, waxes, natural sugars, corn sweeteners, natural and synthetic gums) and specific species (e.g., sodium alginate, polyethylene glycol). These genuses are very large, and include both the compounds mentioned in *Sunshine*, as well as members of the genus recognized by the skilled artisan, including at least:

- FDA approved starches: carboxymethyl starch, sodium starch glycolate, starch, starch 1500 pregelatinized, starch 1551, corn starch, pregelatinized starch, pregelatinized corn starch, potato starch, pregelatinized tapioca starch, rice starch, tapioca starch, and wheat starch;
- the waxes: carnauba wax, wax blend, emulsifying wax, dehydag wax, microcrystalline wax, white wax, yellow wax, beeswax, synthetic beeswax, and candelilla wax;
- the natural sugars: dextrose, high fructose corn syrup, and sucrose; and
- the gums: guar gum, rosin gum, natural gum and xanthan gum.

Inactive Ingredient Guide, Division of Drug Information Resources, Food and Drug Administration (1996). Moreover, known "binders" include at least:

- FDA approved binders alginic acid, cellulose, hydroxyethylcellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyethylene oxide.

Id. There is no suggestion in *Sunshine* that polyethylene glycol should be chosen from this extensive list of compounds, the kind of "needle in the haystack" disclosure held insufficient to support an obviousness rejection in *Luvisi.* Accordingly, the mere mention

of polyethylene glycol in *Sunshine* does not render the instant invention obvious because *Sunshine* does not provide the motivation to select polyethylene glycol required for *prima facie* obviousness.

The laundry list of compounds disclosed in *Sunshine* is analogous to disclosure of a genus of compounds that could be included in a composition, and polyethylene glycol is a species falling with that genus. The disclosure of a genus does not render obvious every species falling within that genus. "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." *In re Baird*, 16 F.3d 380, 382 (1994); also see *In re Duel*, 51 F.3d 1552 (1995). A similar rule appears in the MPEP which states that "[t]he fact that a claimed species or subspecies is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." MPEP § 2144. In *Baird*, the Federal Circuit held that the disclosure of a genus of diphenols did not render obvious one species falling within that genus. *Id.* at 382. The disclosure of the genus did not render obvious the later claimed species because, "there is nothing in the disclosure of Knapp suggesting that one should select such variables." In *Duel*, the Federal Circuit followed the reasoning of *Baird* finding that the disclosure of a protein sequence, and thus of a genus of DNAs that could encode the protein, did not render obvious a DNA that actually encoded the protein "unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared." *Duel*, 41 F.3d. at 1558-59. In the instant case, there is nothing in either *Sunshine* or *White* that would lead one to select polyethylene glycol from among the numerous species disclosed. Accordingly, a

composition comprising ibuprofen, diphenhydramine, and polyethylene glycol is not obvious in view of *Sunshine* and *White*.

Sunshine not only fails to provide motivation to select polyethylene glycol, *Sunshine* actually teaches away from inclusion of polyethylene glycol. *Sunshine* teaches compositions containing ibuprofen and diphenhydramine but lacking polyethylene glycol. *See* Example 1. Moreover, the compositions claimed by *Sunshine* do not recite polyethylene glycol, or any other binder. Finally, the benefits of polyethylene glycol in a composition comprising ibuprofen and diphenhydramine were not contemplated in *Sunshine*. Therefore, *Sunshine* not only fails to motivate one skilled in the art to select polyethylene glycol from the laundry list of compounds it describes, it teaches compositions containing ibuprofen and diphenhydramine that lack polyethylene glycol.

White fails to compensate for *Sunshine*'s lack of motivation to select polyethylene glycol, because like *Sunshine*, it teaches away from the instant invention. *White* states that, "[p]revious solvent systems utilized common solvents such as propylene glycol and polyethylene glycols; each providing excellent solvency but neither being completely appropriate for an important category of pharmaceutically acceptable active agents, the nonsteroidal anti-inflammatory compounds." *White*, col. 1, line 66 to col. 2, line 4. (emphasis added). Accordingly, *White* teaches that polyethylene glycol is not a desired compound for use with NSAIDs and one skilled in the art would be dissuaded from using polyethylene glycol with ibuprofen and diphenhydramine. Consistent with this teaching, the sole example in *White* of a composition containing ibuprofen and

diphenhydramine lacks polyethylene glycol. *White*, Example IV. *White* also teaches away from polyethylene glycol as merely an "optional component that may be used to solubilize certain pharmaceutical actives." *White*, col. 6, line 41. In fact, *White* describes polyethylene glycol as useful to "facilitate dissolution of highly water soluble pharmaceutically acceptable actives that have modest to low solubility in the tri-ester component of the present invention." Column 7, lines 24-28. Therefore, the only teaching of *White* that suggests an advantage of polyethylene glycol is to enhance solubility in the tri-esters of *White* and the only claim of *White* that includes polyethylene glycol, claim 15, is directed to the use of either polyethylene glycol or water in a composition containing a tri-ester. *White* does not contemplate the advantages of polyethylene glycol for preventing the negative interaction between ibuprofen and diphenhydramine disclosed in the instant application. One of ordinary skill in the art would not be motivated by *White* to include polyethylene glycol in a composition comprising ibuprofen and diphenhydramine, unless the composition contained a tri-ester, a component that is not required in composition of any of the instant claims. Accordingly, *White* does not teach or suggest the subject matter of claims 6-13, and fails to provide the motivation for the selection of polyethylene glycol lacking from *Sunshine*.

The Office states that "Sunshine et al. do not teach the composition formulated in a soft gelatin capsule" but appears to rely on *White* for providing the motivation to use the claimed composition in soft gelatin capsules. Office action, p. 3. As described in detail above, *White*, fails to specifically disclose a composition comprised of ibuprofen,

diphenhydramine and polyethylene glycol, *White* provides no motivation to make such a composition, and actually teaches away from such a composition. Additionally, *White* does not teach or suggest formulating this composition in a soft gelatin capsule. In fact, the sole example in *White* of a soft gelatin capsule containing ibuprofen and diphenhydramine lacks polyethylene glycol. *White*, Example IV. Accordingly, *White* would not motivate one of ordinary skill in the art to formulate a composition which contains ibuprofen, diphenhydramine and polyethylene glycol in a soft gelatin capsule as *White* neither teaches nor suggests such a composition nor teaches or suggests the composition formulated in a soft gelatin capsule.

Applicants submit that *Sunshine* and *White* provide no motivation to arrive at the claimed composition comprising ibuprofen, diphenhydramine and polyethylene glycol and actually teach away from the inclusion of polyethylene glycol. Furthermore, *White* provides no motivation to formulate such a composition in a soft gelatin capsule. In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claims 6-13 and 26.

Rejection of Bilayer Tablet Claims

The Office rejects claims 1 and 7-13 under 35 USC § 103(a) as allegedly unpatentable over *Sunshine* in view of U.S. Patent No. 5,512,300 ("*Weng*") and further in view of U.S. Patent No. 6,287,600 ("*Ouali*"). Office Action, p. 4. The Office alleges that it would have been obvious for one of ordinary skill in the art to separate diphenhydramine and ibuprofen of *Sunshine* in a bilayer tablet because *Weng* teaches

that such a composition could have stability problems and *Ouali* provides the motivation to use a bilayer tablet to physically separate the two compounds. *Id.* at 5 and 6.

Applicants respectfully traverse the obviousness rejection of claims 1 and 7-13. Applicants have inserted ", and wherein the ibuprofen is not enterically coated" into claim 1. A composition comprising ibuprofen and diphenydramine wherein the ibuprofen is not enterically coated is neither taught nor suggested by *Sunshine*, *Weng* or *Oauli*, or the combination of these publications. Applicants submit that the Office has failed to establish a *prima facie* case of obviousness because there is no motivation in any of the references to modify or combine their teachings. As stated by the Office, "Sunshine *et al.* do not teach the separation of ibuprofen and diphenhydramine in bilayer tablet formation." *Id.* at 5. In fact, *Sunshine* teaches tablets in which the ibuprofen and diphenhydramine are in the same layer. *Sunshine*, col. 7, line 68 to col. 8, line 13. One of skill in the art would have predicted that the layered tablets of *Sunshine* would not prevent the negative interaction between ibuprofen and diphenhydramine. *Weng* and *Ouali* do not cure the deficiencies of *Sunshine*. *Weng* discusses methods for preparing ibuprofen granulations which exhibit improved stability and resistance to the formation of low melting point eutectics. *See* Abstract and column 3, lines 44-57. *Weng*, however, fails to teach or suggest separating ibuprofen from another substance and focuses on preparing stabilized ibuprofen through chemical treatment. *Weng* provides no working examples comprising ibuprofen and diphenhydramine or working examples of the separation of ibuprofen and diphenhydramine into different layers of a bilayer tablet. Therefore, based on *Weng*,

one of ordinary skill in the art might be motivated to use chemically treated ibuprofen in combination with diphenhydramine, but not a bilayer tablet to separate the two. In fact, because *Weng* provides a potential solution to interaction between ibuprofen and diphenhydramine, one of ordinary skill in the art would not be motivated to solve this problem through use of a bilayer tablet.

The Office appears to rely on *Ouali* as providing the motivation to separate the ibuprofen from diphenhydramine. *Ouali* discusses a composition containing an NSAID and a prostaglandin, but teaches that prostaglandins are unstable compounds in the presence of NSAIDs. *Ouali*, col. 1, line 59. However, *Ouali* does not teach that a bilayer tablet is sufficient to prevent the interaction between NSAIDs and prostaglandins, but teaches that enteric coating of the NSAID solves the problem. The bilayer tablets of *Ouali* are "comprised of two discrete regions, wherein the enterically coated NSAID is present in a first region..." col. 4, line 1. *Ouali* further states that "The NSAID is enterically coated within the stabilized composition of the invention." col. 4, line 52. The steps for manufacturing the tablets state that "[o]nce in particulate form, the NSAID is enterically coated," prior to incorporation in the dosage form. *Ouali*, col. 7, line 18. *Ouali* actually teaches that the enteric coating solves the problem of the interaction between the NSAID and the prostaglandin and that a bilayer tablet is not even necessary.

> In an alternative embodiment, the enterically coated NSAID and the stabilized prostaglandin are mixed into a single granulation, and the admixture is compressed into a tablet or filled into a capsule. In the admixture, there is a random possibility of the NSAID and the prostaglandin coming into

> contact with each other. However, the enteric coating on the NSAID granules provides a physical barrier between the NSAID and the prostaglandin, thereby minimizing direct physical contact between the two active agents.

Ouali, col. 7, line 51 (emphasis added).

Therefore, *Ouali* teaches that the interaction between an NSAID and prostaglandin is prevented by the enteric coating. *Ouali* does not suggest that the NSAID should lack enteric coating and provides no motivation for the skilled artisan to combine the teaching of *Sunshine* with that of *Weng*, while at the same time removing the enteric coating on the NSAID taught in Ouali.

To one of ordinary skill in the art, *Ouali* would not suggest that merely separating an NSAID into a separate layer is sufficient to prevent its negative interaction with other compounds, as the bilayer tablets described in *Ouali* always contain enteric coating of the NSAID. If a bilayer tablet formulation of *Ouali* was made by pressing a layer comprised of non-coated NSAID with a layer comprised of prostaglandin, there would still be potential for the NSAID to induce degradation of the prostaglandin at the interface of the two layers. *Ouali* does not teach that merely separating the NSAID from the prostaglandin in a bilayer tablet is a suitable solution, as the working examples of *Ouali* all use enterically coated NSAIDs. If one skilled in the art were motivated to combine the teaching of *Ouali* with that of *Sunshine* or *Weng*, one would arrive at a composition in which the NSAID is enterically coated, or chemically treated. A chemically treated NSAID is not required by claims 1 or 7-13, and enteric coating is expressly excluded by Applicants' amendments.

The instant invention is directed in part toward addressing the need in the art for compositions allowing a person to fall asleep more rapidly (*See* specification, page 2, line 18). The rapidly acting compositions of the claimed invention are based on the pharmacokinetic profile of ibuprofen. (*See* specification, from page 16, line 20 to page 17, line 1). Patients administered the composition of the instant invention exhibited improvement in "cumulative percent asleep at 60 minutes, ease of falling asleep, duration of sleep, and global evaluation," and the results on sleep duration were surprising. (*See* specification, page 29, lines 9-11, Examples 3-5 and Tables 3-5).

Ouali teaches that coating the NSAID results in a composition that releases the drug in the intestine, but remains intact in the stomach. (*See*, column 3, lines 29-32 and column 4, lines 52-58). Therefore, the effect of enterically coated NSAIDs is delayed by the additional time required for the NSAID to pass from the stomach to the intestine. *Ouali* does not suggest a solution to the problem of *Weng*, as one of skill in the art wishing to make a rapidly acting composition would not formulate the ibuprofen in a manner that could delay its effect in rapidly inducing sleep.

Applicants submit that *Sunshine*, *Weng* and *Ouali* provide no motivation to arrive at the claimed composition which contains ibuprofen and diphenhydramine in a bilayer tablet wherein the ibuprofen is not enterically coated, as they teach coating or chemical modification of an NSAID. In view of the foregoing, Applicants respectfully request the withdrawal of the rejection of claims 1, 7-13 and 26.

Rejection of claims 27-30

The Office rejects claims 27-30 under 35 USC § 103(a) as allegedly unpatentable over *Sunshine* in view of U.S. Patent No. 5,512,300 ("*Weng*") and further in view of U.S. Patent No. 6,287,600 ("*Ouali*") and "Drug Facts and Comparisons" ("Drug Facts"). Office Action, p. 6. The Office states that *Sunshine* teaches that derivatives of proprionic acid include "inflammatory drugs having free -CH(CH3)COOH." Office Action, page 6. The Office further contends that *Sunshine* teaches that the formulation can include "any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch cellulose and carboxymethylcellulose." *Id.* at 6-7. The Office also states that "Sunshine *et al.* do not teach the onset of action within sixty minutes." *Id.* at 7. However, the Office asserts that Drug Facts teaches that the onset of action of diphenhydramine occurs within 25 to 30 minutes, while the onset of action of ibuprofen is half an hour. *Id.* at 7. According to the Office, "it would have been obvious to one of ordinary skill in the art that the composition comprising ibuprofen and diphenhydramine as modified by Weng *et al.* and Ouali *et al.* would have an effect within 60 minutes as claimed by the Applicants because Drug Facts and Comparison teaches that each of the active agents have an onset within 30 minutes." *Id.*

Applicant's respectfully traverse. It would not be obvious to one of ordinary skill to use ibuprofen free acid, despite any teaching in *Sunshine*, because *Weng* and common knowledge teach away from its use in the claimed composition. As noted by the Office, *Weng* teaches a negative interaction between ibuprofen and diphenhydramine in solid dosage forms. *Id.* at 5. The only solution to the negative interaction between ibuprofen and diphenhydramine, prior to the instant invention, is

proposed by *Weng*. However, the *Weng* method converts the ibuprofen to a salt. (*See* abstract of Kararli *et al.* "Solid State Interaction of Magnesium Oxide and Ibuprofen to Form a Salt," Pharm. Res. 6: 804-808 (1989)), cited on the face of *Weng*, which teaches that mixing magnesium oxide and ibuprofen results in formation of an ibuprofen-magnesium salt). Moreover, as noted by the instant specification, the acid moiety of ibuprofen may interact with the basic moiety of diphenhydramine. (*See* Specification, page 12, lines 10-12). *Weng* neutralizes the ibuprofen acid, suggesting that the problem of the negative interaction is due to ibuprofen's acid moiety. In addition, interactions between acids and bases are well known in the art. Accordingly, the mere mention of ibuprofen free acid in *Sunshine* would not motivate one of ordinary skill in the art to select the free acid. On the contrary, from the teaching of *Weng*, combined with common knowledge, one of skill in the art would be motivated to avoid the free acid.

There is no mention in *Sunshine* that calcium stearate, croscarmellose sodium, glyceryl behenate, lactose, microcrystalline cellulose, silicon dioxide colloidal, sodium lauryl sulfate, sodium starch glycolate, corn starch, preglatinized starch, starch or stearic acid polyethylene glycol should be included in a formulation comprising ibuprofen and diphenhydramine. Moreover, *Sunshine* does not teach that these compounds fall within the "inert carriers" disclosed. Therefore, the mere mention of "inert carriers" in *Sunshine* does not render the instant composition obvious because *Sunshine* does not actually disclose all of these compounds and fails to provide the motivation to arrive at the claimed composition.

The claimed composition is not obvious in view of *Weng* and *Ouali* because *Ouali* teaches a composition comprising an enterically coated NSAID. Applicants have amended claims 27-30 to exclude enteric coating of the NSAID. *Ouali* teaches that coating the NSAID results in a composition that releases the drug in the intestine, but remains intact in the stomach. (*See*, column 3, lines 29-32 and column 4, lines 52-58). Therefore, the onset of action of enterically coated NSAIDs is delayed by the additional time required for the NSAID to pass from the stomach to the intestine. A composition comprising an enterically coated NSAID would not exhibit the properties taught in Drug Facts as the enteric coating would delay the action of the active ingredients. Accordingly, the claimed rapidly acting composition is not obvious in view of *Weng* and *Ouali*.

Conclusion

In view of the foregoing, Applicants submit that claimed invention is not obvious in view of the cited art and that the pending claims are in condition for allowance. Applicants request reconsideration and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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